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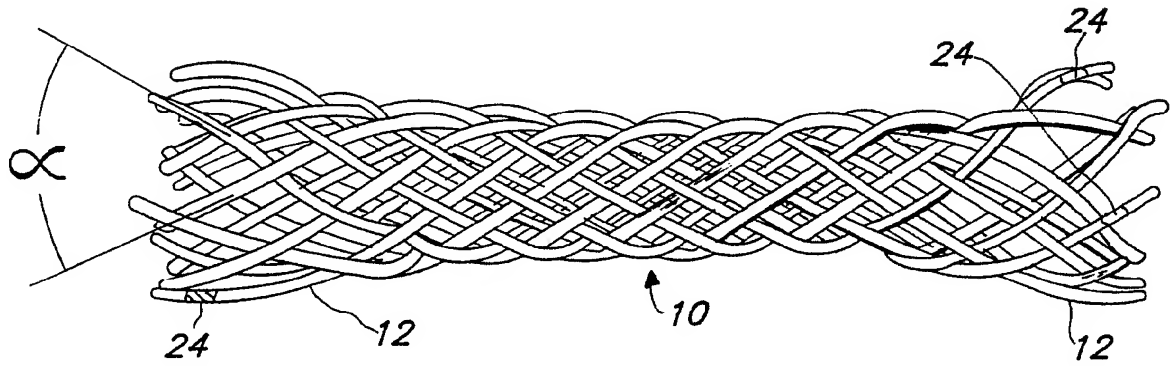

(57) Abstract

A prosthesis for insertion into a lumen to limit restenosis of the lumen. The prosthesis carries restenosis-limiting drugs which elute after the device is positioned in the lumen.

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INTRALUMENAL DRUG ELUTING PROSTHESIS

Background of the Invention

1. Field of the Invention

This invention relates to methods for lessening restenosis of body lumens, and to prostheses for delivering drugs to treat said restenosis.

2. Description of the Related Art

Restenosis is defined as the enclosure of a previously dilated, ablated, or lased peripheral or coronary vessel. It occurs at a rate of 20-50% for each of these procedures and is dependent on a number of variables (i.e., vessel location, lesion length, etc.). Restenosis may begin immediately following an angioplasty procedure, but ceases at the end of approximately six (6) months. There is not a current therapeutic procedure that has been proven to significantly reduce this restenosis rate.

A recent technology that has been developed that assesses the problem of restenosis is intravascular stents. Stents are metallic devices that are permanently implanted (expanded) in coronary and peripheral vessels. The goal of these stents is to provide a long-term "scaffolding" or support for the diseased (stenosed) vessels. The theory being, if you can support the vessel from the inside, the vessel will not close down or restenose. Unfortunately, initial data from clinical stent implants shows that these metallic structures do not significantly reduce the amount of restenosis.

Many pharmacologic (biochemical) attempts have been made to reduce the amount of restenosis. All of these attempts have dealt with the systemic delivery of drugs via oral or intravascular introduction. Very limited success has been achieved with this systemic approach.

For drug delivery , it has been recognized for a long period of time that pills and injections may not be the best mode of administration. It is very difficult with these types of administration to get constant drug delivery. Through repeated doses, these drugs often cycle through concentration peaks and valleys, resulting in time periods of toxicity and ineffectiveness. Thus, localized drug treatment

is warranted.

The art described in this section is not intended to constitute an admission that any patent, publication or other information referred to herein is "prior art" with respect to this invention, unless specifically designated as such. In addition, this section should not be construed to mean that a search has been made or that no other pertinent information as defined in 37 C.F.R. § 1.56(a) exists.

Summary of the Invention

The invention provides prostheses which may be inserted into a lumen of a body and fixed to the lumen wall adjacent an area needing treatment. Most typically, the lumen will be part of the vascular system which may restenose. However, the methods and devices of the invention are also suited to treatment of any body lumen, including the vas deferens; ducts of the gallbladder, prostate gland, trachea, bronchus and liver or any other lumen of the body where medication cannot be applied without a surgical procedure. The invention applies to acute and chronic closure or reclosure of body lumens.

The prostheses of the invention include at least one drug which will release from the device at a controlled rate to supply the drug where needed without the overkill of systemic delivery. The prostheses include means for fixing the device in the lumen where desired. The prostheses may be completely biodegradable or may be bioabsorbable in whole or in part such that the prostheses will be completely incorporated into the lumen wall as a result of tissue growth, i.e. endothelialization. Alternatively, the prostheses may be biostable in which case the drug is diffused out from the biostable materials in which it is incorporated.

The prosthesis comprises a generally flexible tubular body which is fixed against the lumen walls by a mechanical action. The device should not cause an appreciable reduction in the lumen cross-section where inserted. Conventional stent designs which provide an

expansion of the vessel are suitable, though not required. In all cases, the prostheses of the invention require the presence of an elutable drug compounded to the prosthesis itself. With conventional metal stents, the invention requires a drug-carrying coating overlying at least a portion of the metal.

The drugs in the prosthesis may be of any type which would be useful in treating the lumen. In order to prevent restenosis in blood vessels, migration and subsequent proliferation of smooth muscle cells must be checked. Platelet aggregation and adhesion can be controlled with antiplatelets and anticoagulants. Growth factor and receptor blockers and antagonists may be used to limit the normal repair response.

The current invention contemplates the usage of any prosthesis which elutes drugs locally to treat a lumen in need of repair. Controlled release, via a bioabsorbable polymer, offers to maintain the drug level within the desired therapeutic range for the duration of the treatment. When "stent" is referred to herein, it may include the classical definition of stents as they are used in intravascular applications. "Stent" used herein also includes any prosthesis which may be inserted and held where desired in a lumen. It includes, but is not limited to, structures such as those shown and described in U.S. Patent 4,886,062 to Wiktor.

Brief Description of the Drawings

A detailed description of the invention is hereafter described with specific reference being made to the drawings in which:

FIG. 1 is a greatly enlarged side view of an intralumenal drug-eluting prosthesis of the invention;

FIG. 2 is a greatly enlarged side view of an alternative embodiment to the prosthesis of Fig. 1;

FIG. 3A is a greatly enlarged fragment of the embodiment of Fig.1;

FIG. 3B is a greatly enlarged fragment of the embodiment of Fig. 1 in which two layers of polymer are

present, each having a different drug;

FIG. 4 is a greatly enlarged fragment of the embodiment of Fig. 2;

FIG. 5 is a greatly enlarged microscopic fragmentary detail of drug shown eluting from the porous structure of a filament or filament coating in a prosthesis into tissue or the vessel lumen;

FIG. 6 is a greatly enlarged cross-section of a blood vessel showing plaque profile immediately post- balloon catheter dilation procedure;

FIG. 7 is a greatly enlarged cross-section of the subject of Fig. 6 at a later date showing restenosis;

FIG. 8 is a greatly enlarged cross-section of a blood vessel showing plaque-prosthesis profile immediately post-prosthesis implant procedure;

FIG. 9 is a greatly enlarged cross-section of the subject of Fig. 8 after ingrowth has occurred;

FIG. 10 is a greatly enlarged fragmentary perspective view of a blood vessel wall and prosthesis filament of Figs. 1 and 3 immediately after implantation;

FIG. 11 is a greatly enlarged fragmentary perspective view of the subject of Fig. 10 after about one month;

FIG. 12 is a greatly enlarged fragment of a loose weave of prosthesis filaments;

FIG. 13 is a greatly enlarged fragment of a coated metal filament in a loose weave;

FIG. 14 is a greatly enlarged fragment of a melted junction weave of prosthesis filaments in a loose weave;

FIG. 15 is a greatly enlarged fragment of a kinked junction weave of prosthesis filaments;

RW 2/22/90 DEV 2/23/90

FIG. 16 is a greatly enlarged fragment of multi strand weave of prosthesis filaments; and

FIG. 17 is an alternative embodiment to Fig 16, in which the strands are not woven.

Description of the Preferred Embodiments

Restenosis

In the summary, a very simple definition of restenosis was given. As a complement to this definition,

there are several more clinical definitions. Several of these definitions are listed below:

1. Loss of at least 50% of the initial gain achieved in angioplasty.

2. Decrease of at least 30% in the lumen diameter compared to post-angioplasty result.

3. A return to within 10% of the pre-angioplasty diameter stenosis.

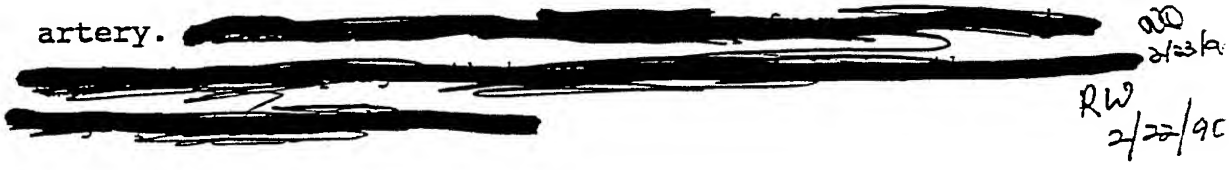
4. An immediate post angioplasty diameter stenosis of less than 50% that increases to 70% or greater at follow-up.

6. Deterioration of 0.72 mm in minimal luminal diameter or greater from post-angioplasty to follow-up.

7. As for 6, but with a deterioration of 0.5 mm.

These definitions are used by cardiologists to clinically (angiographically) define restenosis.

Several hypotheses exist on why and how restenosis occurs. The current, most widely accepted explanation is that restenosis is a natural healing process in response to the arterial injury that occurs during all types of angioplasty procedures. This very complex healing process results in intimal hyperplasia, more specifically migration and proliferation of medial smooth muscle cells (SMC). The problem associated with this arterial healing process is that in some instances, it does not shut off. The artery continues to "heal" until it becomes occluded. It should be noted that restenosis is not a re-deposition of the plaque-like cholesterol material that originally occluded the artery.



The following is a possible scenario for restenosis according to the vessel healing hypothesis. Successful angioplasty of stenotic lesions produces cracking of the plaque, dissection into the media, denudation and destruction of endothelial cells, exposure of thrombogenic collagens, released tissue thromboplastin, and an increased loss of

protacyclin production. All of these lead to the aggregation of active platelets.

Figs. 6 and 7 show a typical vessel 30 in cross-section after angioplasty procedures showing the interior 32 of the lumen. In Fig. 6 the interior of the lumen is rough and includes intimal flaps 34. Damage causes healing with deposition of platelets, fibrin formation and proliferation of neointima 37 which as shown in Fig. 7 significantly reduces the interior of the lumen.

Activated platelets release several mitogens including platelet derived growth factor (PDGF), epidermal growth factor, and transforming growth factor. PDGF has both mitogenic and chemotactic properties and thus, may induce both migration of SMC from the medial layer to the intimal layer as well as proliferation (intimal hyperplasia). PDGF causes SMC proliferation by binding to specific PDGF receptors. Once the PDGF is bound to the receptors, deoxyribose nucleic acid (DNA) synthesis occurs and new cells are replicated. Minor endothelial injury may cause platelet adhesion and activation with the resultant release of PDGF. Thus, even the deposition of a monolayer of platelets may be sufficient to induce SMC proliferation.

Deeper arterial injury which is sometimes associated with complex stenotic lesions leads to more extensive platelet deposition and activation which may cause an even greater availability of the mitogenic factors. Thus, increased SMC proliferation and intimal hyperplasia. Arterial injury from angioplasty may result in release of PDGF-like compounds from not only platelets but also macrophages, monocytes, endothelial cells, or SMC's themselves.

Activated SMC from human atheroma or following experimental arterial injury secrete PDGF-like molecules which appears to lead to self perpetuation of SMC proliferation by the release of their own PDGF-like substances. Thus, any or all of the cells which can secrete PDGF related substances (platelets, macrophages, monocytes, endothelia, and smooth muscle cells) may contribute to the

cascading effect of restenosis after angioplasty.

The previous restenosis scenario resulted from normal angioplasty procedures. During balloon angioplasty if the balloon is undersized or not totally inflated and the plaque cracking and extensive endothelial denudation does not occur the lesion would restenose. Rheologic factors contribute as well to the interaction between platelets and the arterial wall. Residual stenosis, resulting from inadequate balloon expansion, produces a high local shear rate and enhances platelet deposition and activation. These stenoses may be important as a stimulus for some proliferation through enhanced platelet deposition and secretion of growth factors. This hypothesis correlates with the increased incidence of restenosis in patients with high-grade residual stenoses or transtenotic gradients.

Prevention of Restenosis

In order to prevent restenosis, one must stop the proliferation of smooth muscle cells. As stated earlier, this is a biochemical process which cannot be treated mechanically. Several hypotheses exist on how to biochemically stop restenosis. Some of which are:

1. Reduce the adhesion and aggregation of the platelets at the arterial injury site.
2. Block the expression of the growth factors and their receptors.
3. Develop competitive antagonists of the above growth factors.
4. Interfere with the receptor signaling in the responsive cell.
5. Find a "natural" inhibitor of smooth muscle proliferation.

Item #1 is directly related to the formation of thrombus, a major problem with all types of angioplasty procedures. Items #2, #3, and #4 are closely related. They deal with blocking restenosis during the massive cell

migration and replication cycle. Unlike item #1, these items address the growth factors that are produced from sources other than platelets. Item #5 is listed to address the question, why don't the 50-80% of the people who don't restenose, restenose. There may be some type of natural inhibitor that these people produce that stops the proliferation of smooth muscle cells.

There are at least two (2) different ways to prevent the adhesion and aggregation of platelets. One method is to use an antiplatelet and another is to use an anticoagulant.

Antiplatelet drugs include drugs such as aspirin and dipyridamole. Aspirin is classified as an analgesic, antipyretic, anti-inflammatory, antiplatelet drug. It has been clinically tested and proven to reduce the risk of sudden death and/or non-fatal reinfarction in post myocardial infarction (heart attack) patients. The proposed mechanism of how aspirin works, relates directly to the platelets. It somehow blocks the platelets, restricting coagulation. This prevents the cascading platelet aggregation found in thrombus and restenosis. Aspirin is therefore a possible restenosis inhibitor. Dipyridamole is a drug similar to aspirin, in that is has anti-platelet characteristics. Dypridimole is also classified as a coronary vasodilator. It increases coronary blood flow by primary selective dilatation of the coronary arteries without altering systemic blood pressure or blood flow in peripheral arteries. These vasodilation characteristics are thought to be possibly beneficial for restenosis prevention.

Anticoagulant drugs include Heparin, Coumadin, Protamine, and Hirudin. Heparin is the most common anticoagulant used today. Heparin, in one form or another, is used in virtually every angioplasty procedure performed. All four (4) of these drugs function as an anticoagulant by preventing the production of thrombin, a binding agent which causes blood to clot. This too, may reduce the cascading effect of platelet aggregation at the lesion site, thus

possibly reducing restenosis. The use of Protamine in the presence of Heparin causes the Protamine to function as a Heparin antagonist, blocking the effect of the Heparin. Protamine, however, used alone, acts as an anticoagulant. Hirudin is singled out because it is not normally found in the human body. Hirudin is a drug that is found in the salivary glands of leeches. It is a very concentrated anticoagulant that functions in the same manner as Heparin, Coumadin, and Protamine.

There are several types of drugs that interrupt cell replication. Antimitotics (cytotoxic agents) work directly to prevent cell mitosis (replication), whereas antimetabolites prevent deoxyribose nucleic acid (DNA) synthesis, thus preventing replication. The action of the antimitotics and antimetabolites are so similar, they will be grouped into one category. This category will be known as the anti- replicate drugs.

Anti-replicate drugs include among others: Methotrexate, Azathioprine, Vincristine, VinBlastine, Fluorouracil, Adriamycin, and Mutamycin. The target systemic molarity desired with methotrexate is on the order of 10^{-6} M with a range of between 10^{-3} to 10^{-8} Molar. Locally, the molarity of the drug may be highly variable, which is one of the great disadvantages in systemic administration of the drug. When drugs are delivered locally via the prosthesis of the invention, they may be at therapeutic levels at the diseased site while at the lower limits of detectability in the bloodstream. So little drug is required for effective local treatment of a lumen that the drug may not be detectable in blood samples.

If the restenosis process ranges from immediately after injury to about 4 months later, then the generalized elution rates contemplated are that the drug should start to be released immediately after the prosthesis is secured to the lumen wall to lessen cell proliferation. The drug should then continue to elute for about four months in total.

Complex systems of drugs may be carried by the

prosthesis. An anticoagulant or antiplatelet may be included on the outermost surface of the device in order to elute off very quickly for the first several weeks. Antireplicates can be formulated into the device to continue to elute later, when in contact with non-blood cells after neointima overgrowth has surrounded the device. This usually occurs in about two weeks. The drug elution rate does not need to be uniform, and may be tailored to fit the need of the patient.

Prosthesis (Stent) Design

The current invention contemplates the usage of any prosthesis which elutes drugs locally to treat a lumen in need of repair. When "stent" is referred to herein, it may include the classical definition of stents as they are used in intravascular applications. "Stent" used herein also includes any prosthesis which may be inserted and held where desired in a lumen.

Figs. 1 through 17 show features of some of the prostheses which may be used to carry and elute restenosis limiting-drugs.

The current preferred stent 10 configuration consists of a single filar, monofilament braided mesh design as shown in Fig. 1. There are sixteen (16) filaments 12, eight (8) of which are wound in one helical direction, and the remaining eight (8) which are wound in the opposite direction. The stent 10 is self-expanding to a predetermined diameter. The profile (diameter) of the stent 10 can be easily reduced by pulling the stent 10 longitudinally. In this reduced profile configuration, the stent 10 can be loaded into a catheter for delivery into the vessel.

The stent 20 shown in Figures 2 and 4 is a metallic malleable design which may be forced against a lumen wall by a balloon catheter which fixes it into position. The exterior surface of the metal filaments 22 would include a coating 14 with a drug-eluting polymer described previously. The polymer may be biostable or bioabsorbable. If biostable, the drug would diffuse out of the polymer.

The variations of design shown in the embodiments

of Figs. 1 and 2 show that the prosthesis of the invention must be secured against a lumen wall and must carry a drug-eluting polymer.

There are many variables in the design of stent 10. The angle (α) of the filaments 12 is a major variable. The angle α can vary from 0 degrees to 180 degrees. The design in the Figures is based on an angle in the 60 degree to 90 degree range.

There are many options for fabricating the drug eluting stents. One option is to have all sixteen (16) filaments be drug eluting. Or, you could have any number of filaments up to sixteen (16) degrade and elute drugs. Another option is to have a multi-filar stent. Instead of a single filament braided into the stent, it is possible to have two (2), three (3), or even four (4) strands 16 braided to form a filament 12 as shown in Fig. 16. This would create a stent with much greater expansile force, but also have much more material in the surface area. This is a common trade-off in stent design. Similar to the single-filar design, the multi-filar form shown in Fig. 16 could have varying numbers of strands 16 that are drug eluting. Figs. 16 and 17 show that the multi-filar design may be braided or unbraided. One (1), two (2), three (3), or four (4) of the filaments could be impregnated with a drug and biodegradably elute. Alternatively, the polymer may be biostable which allows for diffusion of the drug without degradation.

The stent 10 of Fig. 1 consists of a wound braided mesh which is self-expanding to a predetermined diameter and whose profile diameter can be greatly reduced for catheter introduction. The radial expansile force increases with diameter to the point of the self- expanded diameter limit, at which point the angle between the filaments and the longitudinal axis is a maximum. Figures 12 through 15 show alternative construction techniques to alter the radial expansive force. Figure 12 shows the filaments 12 being woven without any connection. Figure 13 is similar except the filament 22 is formed with a metal core 16 and a coating 14. In Fig. 14 the individual filaments 12 are shown with a bonded juncture 18. The bonding at the junctures 18 prevents

the individual filaments 12 from sliding relative to each other, which improves the radial strength. The mechanically kinked junction 19 shown in Fig. 15 also limits the sliding of the filaments to change the radial strength. A heated platen press may be pressed against the wound stent while still on the forming mandrel to form the kinks. Higher temperatures may be used to form the melted junctures 18.

The devices may be made more visible under fluoroscopy and x-ray by incorporating radiopaque materials into marker bands 24 to the individual filaments 12 at the ends of the stent 10 as shown in Fig. 1. Such bands could help to locate the stent and assure proper placement and patency.

Bioabsorbable Prosthesis (Stent) Materials

Controlled release, via a bioabsorbable polymer, offers to maintain the drug level within the desired therapeutic range for the duration of the treatment. In the case of stents, the prosthesis materials will maintain vessel support for at least two weeks or until incorporated into the vessel wall even with bioabsorbable, biodegradable polymer constructions.

Several polymeric compounds that are known to be bioabsorbable and hypothetically have the ability to be drug impregnated may be useful in prosthesis formation herein. These compounds include: poly-l-lactic acid/polyglycolic acid, polyanhydride, and polyphosphate ester. A brief description of each is given below.

Poly-l-lactic acid/polyglycolic acid has been used for many years in the area of bioabsorbable sutures. It is currently available in many forms, i.e., crystals, fibers, blocks, plates, etc. These compounds degrade into non-toxic lactic and glycolic acids. There are, however, several problems with this compound. The degradation artifacts (lactic acid and glycolic acid) are slightly acidic. The acidicity causes minor inflammation in the tissues as the polymer degrades. This same inflammation could be very detrimental in coronary and peripheral arteries, i.e., vessel occlusion. Another problem associated with this polymer is

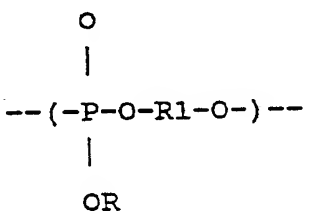
the ability to control and predict the degradation behavior. It is not possible for the biochemist to safely predict degradation time. This would be very detrimental for a drug delivery device.

Another compound which could be used are the polyanhydrides. They are currently being used with several chemotherapy drugs for the treatment of cancerous tumors. These drugs are compounded in the polymer which is molded into a cube-like structure and surgically implanted at the tumor site.

Polyanhydrides have weaknesses in their mechanical properties, due to low molecular weights. This drawback makes them difficult to process into a filament form. Also, polyanhydrides have poor solubility, making characterization and fabrication difficult.

The compound which is preferred is a polyphosphate ester. Polyphosphate ester is a proprietary compound which is currently being developed by Dr. Kam Leong at John Hopkins University (JHU). Similar to the polyanhydrides, polyphosphate ester is being researched for the sole purpose of drug delivery. Unlike the polyanhydrides, the polyphosphate esters have high molecular weights (600,000 average), yielding attractive mechanical properties. This high molecular weight leads to transparency, and film and fiber properties. It has also been observed that the phosphorous-carbon-oxygen plasticizing effect, which lowers the glass transition temperature, makes the polymer desirable for fabrication.

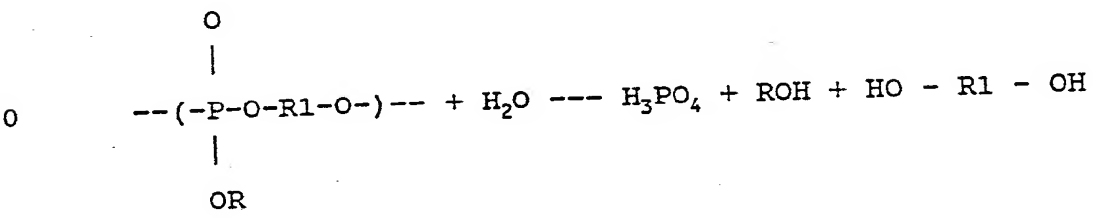
The basic structure of polyphosphate ester monomer is shown below.



where P corresponds to Phosphorous,

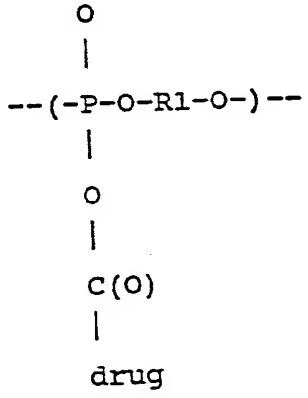
O corresponds to Oxygen,
and R and R1 are functional groups.

Reaction with water leads to the breakdown of this compound into monomeric phosphates (phosphoric acid) and diols (see below).

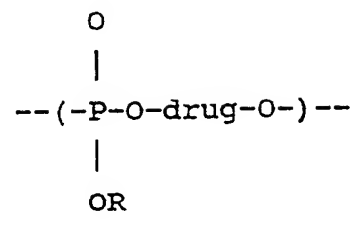


It is the hydrolytic instability of the phosphorous ester bond which makes this polymer attractive for controlled drug release applications. A wide range of controllable degradation rates can be obtained by adjusting the hydrophobicities of the backbones of the polymers and yet assure biodegradability.

The functional side groups allow for the chemical linkage of drug molecules to the polymer. This is shown below.



The drug may also be incorporated into the backbone of the polymer.



In summary, the highly hydrolytically reactive phosphorous ester bond, the favorable physical properties, and the versatile chemical structure make the polyphosphate esters a superior drug delivery system for a prosthesis.

Figs. 3A and 3B show that the filaments 12 may be made from one or several layers of polymer. In Fig. 3A only a single polymer is present to carry the drugs. In Fig. 3B a second layer of polymer 15 is shown. That layer 15 may be a simple barrier which limits diffusion of drugs in the polymer 14. In that event, the smaller molecules could elute out immediately, while larger compounds would not elute until later when the layer 15 has biodegraded. Alternatively, layer 15 may include a different drug incorporated therein from that found in layer 14. The barrier coating 15 could be as simple as a silicone or polyurethane.

Operation

The prosthesis is inserted into the lumen wherever needed as per the usual procedure for stents. The device is fixed into place either by radial expansion in devices such as shown in Fig. 1 or are deformed by a balloon catheter in the case of devices in accordance with Fig. 2.

Figures 8 through 11 show the placement and effects of the drug-eluting prosthesis of the invention. The prosthesis tacks up any intimal flaps and tears caused by any prior ballooning. The initial deposition of platelets and subsequent thrombus formation 38 is controlled and minimized by the stent design and the elution of drug which limits platelet aggregation and other immediate repair responses described previously. Localized thrombus formations in the areas of cracked and roughened plaques and newly exposed underlying collagen and fibro-muscular tissues is also decreased. This results in limited but quick neointima formation 40 and intimal proliferation over individual stent

filaments progressing to mature endothelial lining. Long term restenosis is therefore limited. Elution of the anti-replicates alone or in conjunction with the initial elution of anti-coagulants can also limit the restenosis which occurs in the natural healing process.

While this invention may be embodied in many different forms, there are shown in the drawings and described in detail herein specific preferred embodiments of the invention. The present disclosure is an exemplification of the principles of the invention and is not intended to limit the invention to the particular embodiments illustrated.

This completes the description of the preferred and alternate embodiments of the invention. Those skilled in the art may recognize other equivalents to the specific embodiment described herein which equivalents are intended to be encompassed by the claims attached hereto.

WHAT IS CLAIMED IS:

1. An intralumenal drug-eluting prosthesis comprising:

a prosthesis having means for fixing said prosthesis to an interior of a lumen, said prosthesis being constructed and arranged such that at least a portion of the exterior surface of said prosthesis is formed from a polymer into which a drug which limits acute or chronic closure is compounded.

2. The prosthesis of Claim 1 wherein said prosthesis includes at least two separate layers of polymers, each of said layers including a different drug compounded therein.

3. The prosthesis of Claim 1 wherein said drug is selected from the group consisting of antiplatelet drugs, anticoagulant drugs, anti-inflammatory drugs, antimetabolite drugs and combinations of said drugs.

4. The prosthesis of Claim 1 wherein said polymer is bioabsorbable.

5. The prosthesis of Claim 1 wherein said prosthesis is a self-expanding stent.

6. An intralumenal drug-eluting prosthesis comprising:

a stent having a radially and axially flexible, elastic body that is variable under axial movement of ends of the body relative to each other, said stent being composed of a plurality of thread elements each of which is woven in a helix configuration along the center line of the body as a common axis, said body including elements wound in opposing helical directions; and

said stent including a drug compounded into the outer surface of at least one of said elements.

7. The prosthesis of Claim 6 wherein at least one of said elements includes several monofilaments.

8. The prosthesis of Claim 7 in which the elements are monofilaments of a bioabsorbable polymer.

9. The prosthesis of Claim 6 wherein said elements are formed from a metal which is coated with a bioabsorbable polymer into which said drug is compounded.

10. The prosthesis of Claim 6 further including a barrier coating over at least one of said elements into which a drug is compounded, said coating limiting the diffusion of the drug out of the prosthesis.

11. The prosthesis of Claim 6 wherein said drug is selected from the group consisting of antiplatelet drugs, anticoagulant drugs, antimetabolite drugs and combinations of said drugs.

12. The prosthesis of Claim 6 wherein said at least one of said elements includes an anticoagulant drug compounded therein and at least one element includes an antimetabolite drug compounded therein.

13. A method for decreasing restenosis in an animal lumen comprising the steps of:

(a) inserting a prosthesis compounded with at least one restenosis-limiting drug into a lumen at the point where restenosis may occur; and

(b) fixing said prosthesis to said lumen such that it will stay rigidly in place.

14. A method for treating a lumen in a body in need of treatment comprising the steps of:

(a) inserting a prosthesis into the lumen in need of treatment at the area where treatment is needed, said prosthesis being compounded with at least one drug effective in treating the lumen; and

(b) fixing said prosthesis to said lumen such that it will stay where positioned.

15. A method for limiting acute or chronic lumen closure in an animal lumen comprising the steps of:

(a) inserting a bioabsorbable stent compounded with at least one lumen closure-limiting drug into a lumen at the point where closure may occur;

(b) expanding said stent against the walls of the lumen to provide support to the lumen; and

(c) allowing said stent to naturally bioabsorb to provide a controlled release of said at least one drug.

16. An intralumenal drug-eluting prosthesis comprising:

a generally tubular prosthesis having means for fixing said prosthesis to an interior of a lumen, said prosthesis being constructed and arranged such that at least a portion

of the exterior surface of said prosthesis is formed from a polymer into which a drug which limits acute or chronic closure is compounded.

FIG. 1

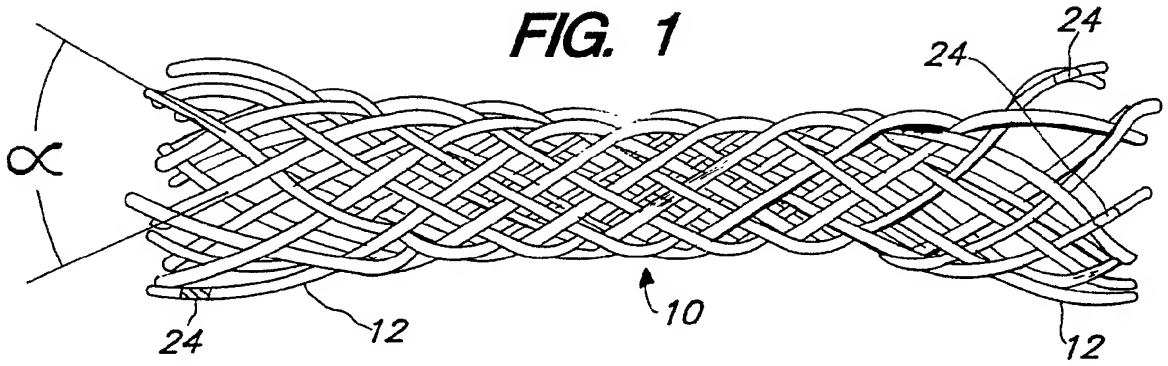


FIG. 2

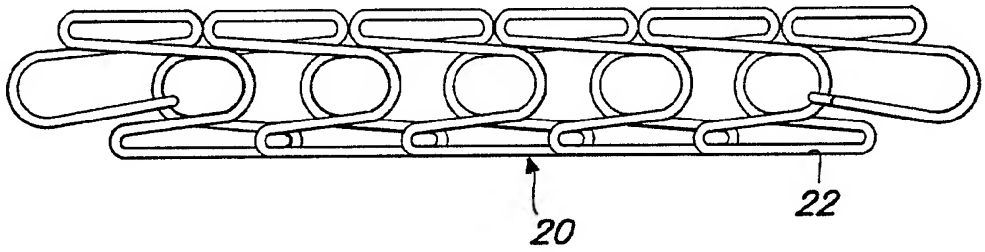


FIG. 3A

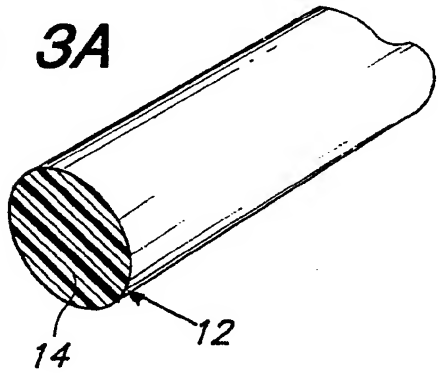


FIG. 4

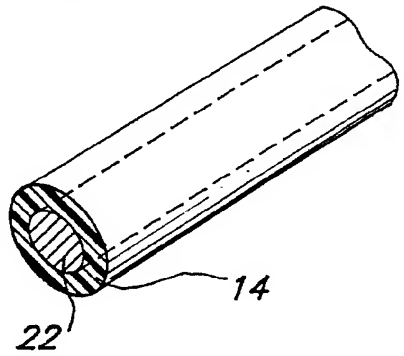


FIG. 5

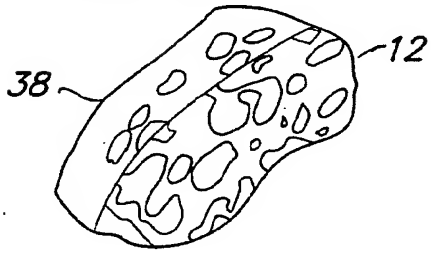


FIG. 3B

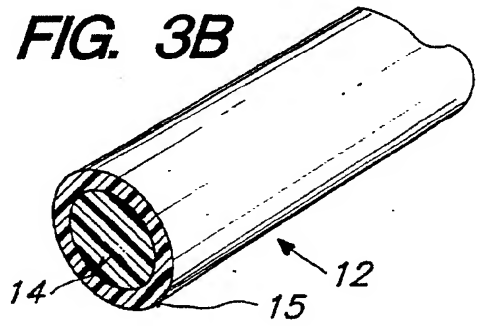


FIG. 6

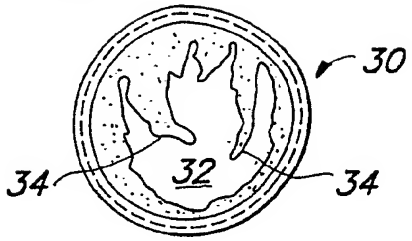


FIG. 7

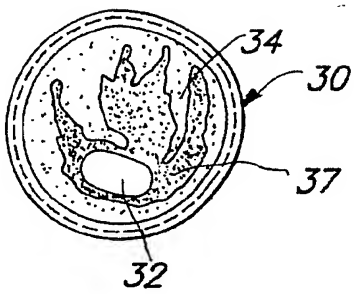


FIG. 8

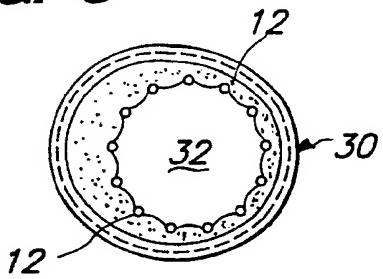


FIG. 9

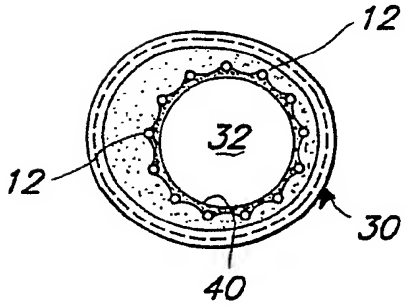


FIG. 10

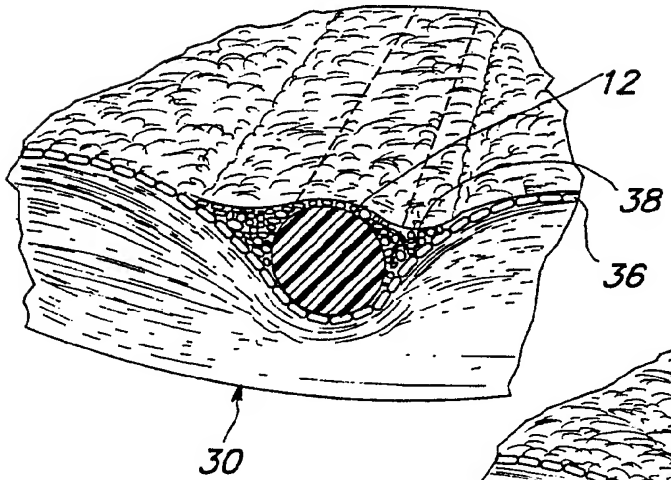


FIG. 11

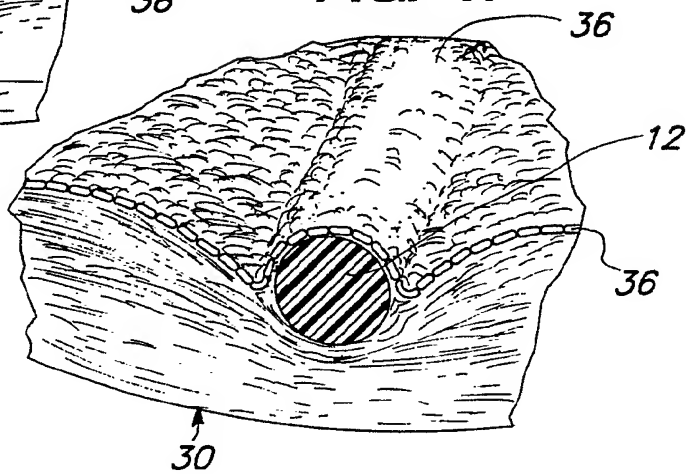


FIG. 12

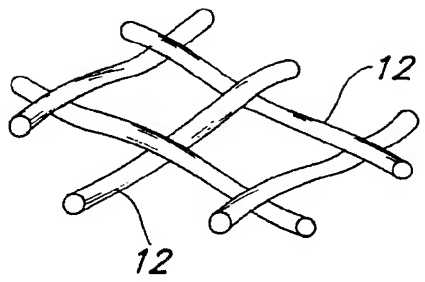


FIG. 13

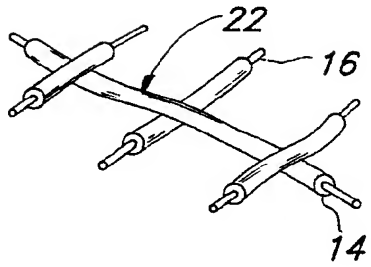


FIG. 14

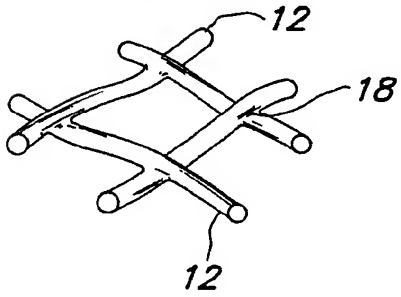


FIG. 15

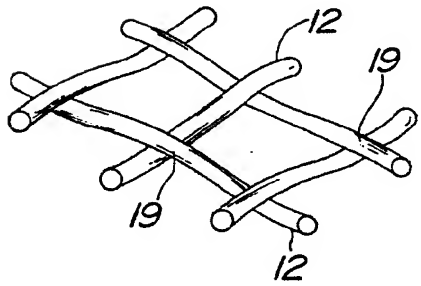


FIG. 16

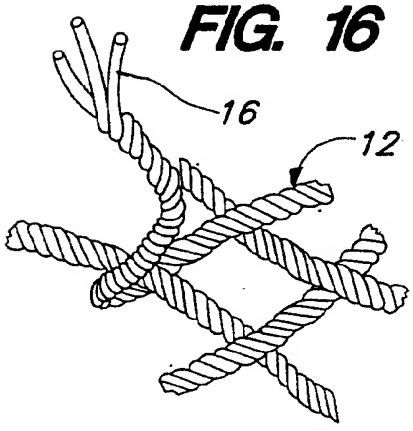
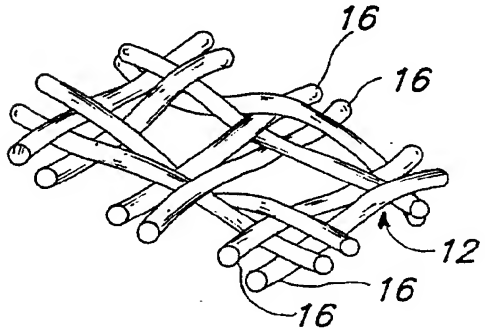


FIG. 17



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/01097

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 F 2/04, 2/06, A 61 M 31/00, A 61 L 27/00, A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 F; A 61 M; A 61 L; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	WO, A1, 9013332 (CEDARS-SINAI MEDICAL CENTER) 15 November 1990, see page 5, line 23 - page 6, line 38 claims	1,3-5, 16
	--	
X	WO, A1, 8903232 (BUKH MEDITEC A/S) 20 April 1989, see page 4, line 15 - page 7, line 26; page 9, line 8 - line 16; page 13, line 28 - page 16, line 21	1-4, 16
Y		5-10
	--	
X	US, A, 4678466 (P L ROSENWALD) 7 July 1987, see column 3, line 40 - column 4, line 2; column 4, line 50 - line 64	1,16
Y		2-10
	--	

* Special categories of cited documents: [10]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th June 1991	10 JUL 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T. TAZELAAR

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 4886062 (D M WIKTOR) 12 December 1989, see column 2, line 35 - column 3, line 50 cited in the application	2-10
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Y	GB, A, 2153235 (MEADOX MEDICALS INC) 21 August 1985, see page 1, line 50 - page 2, line 6; page 2, line 23 - line 50	1-10, 16
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/01097

SA 45914

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 29/05/91
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9013332	15/11/90	US-A-	4923415	08/05/90
		US-A-	4975089	04/12/90
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US-A- 4678466	07/07/87	US-A-	4484922	27/11/84
US-A- 4886062	12/12/89	AU-D-	2378488	20/04/89
		EP-A-	0312852	26/04/89
		JP-A-	1145076	07/06/89
GB-A- 2153253	21/08/85	DE-A-	3502789	08/08/85
		JP-A-	60180112	13/09/85
		NL-A-	8500231	16/08/85
		US-A-	4549913	29/10/85